APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Xylenes (mixed xylenes, *ortho-*, *meta-*, and *para*-xylenes)
CAS Numbers: 1330-20-7, 95-47-6, 108-38-3, 106-42-3
Date: August 2007
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 49
Species: Human

Minimal Risk Level: 2 [ ] mg/kg/day [X] ppm
[Note: A single acute-duration inhalation MRL has been derived based on data for *m*-xylene that applies to mixed xylenes and all of the individual isomers. The justification for deriving a common value is that the isomers have similar toxicokinetic properties and elicit similar toxicological effects, with no isomer consistently exhibiting the greatest potency, depending on the end point. Further discussion of this rationale is presented in Section 3.2.]

Reference: Ernstgard L, Gullstrand E, Lof A, et al. 2002. Are women more sensitive than men to 2-propanol and *m*-xylene vapors? Occup Environ Med 59:759-767.

Experimental design: Fifty-six healthy volunteers (28 per sex) between the ages of 20 and 49 years were exposed to 50 ppm (200 mg/m^3) *m*-xylene, clean air (controls), or 150 ppm 2-propanol in a dynamic exposure chamber for 2 hours. Each subject experienced the three treatments. Sessions were separated by intervals of 2 weeks. The experiment was initially designed to be balanced with two men and two women exposed on each occasion with all six possible orders of treatment represented. (Schedule changes by the volunteers resulted in imbalances in treatment orders, but ANOVA analysis indicated that the imbalance had no significant effect on the results.) Subjects rated the level of perceived discomfort using a visual analog scale (0–100 mm) in a questionnaire with 10 questions during exposure (3, 60, and 118 minutes from the start of exposure), and post-exposure (140 and 350 minutes from onset). Items included discomfort in eyes, nose, throat, or airways; breathing difficulty; solvent smell; headache; fatigue; nausea; dizziness; and feeling of intoxication. Pulmonary function measurements were conducted via spirometer prior to exposure, immediately after exposure, and 3 hours post-exposure. These included vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), and forced expiratory flow in 25, 50, or 75% of FVC (FEF_{25}, FEF_{50}, FEF_{75}). Nasal swelling was assessed by acoustic rhinometry before, immediately after, and 3 hours after the end of exposure. Nasal lavages obtained before and 3 hours after the end of exposure were evaluated for markers of inflammation (lysozyme, albumin, myeloperoxidase, and eosinophilic cationic protein). Eye blinking was measured throughout exposure by electromyography and color vision was assessed before, immediately after, and 3 hours post-exposure.

Effect noted in study and corresponding doses: Statistically significant increases, compared to air-exposure, in the average rating of self-reported symptoms resulting from exposure to *m*-xylene at 50 ppm were observed for discomfort in the eyes and nose, detection of solvent smell, and feeling of intoxication in both sexes after 60 and 118 minutes, in discomfort in the throat or airways in women after 60 minutes, in breathing difficulty and nausea in men at 118 minutes and women at both timepoints, in headache and fatigue in men at both timepoints, and in dizziness in men at 118 minutes. All of the statistically significant increases in the subjective ratings were minimal except for detection of solvent smell, which was moderate.

Statistically significant minimal changes, compared to air-exposure, were observed in objective measures of respiratory function (percent change from pre-exposure measurements) in women, but not men, 3 hours after the end of the exposure to *m*-xylene: FVC reduced by 2.81% (compared to reduced by 0.06% for air exposure, $p<0.01$), FEV_1/FVC increased by 1.09% (compared to decreased by 0.34% for air exposure, $p<0.03$), and FEF_{75} increased by 3.32% (compared to decreased by 5.53% for air exposure, $p<0.04$). No statistically significant change was observed immediately after exposure. Irrespective of exposure condition, there were diurnal changes in lung function (FVC and FEV_1) that were more pronounced in women than in men. There were no solvent-related changes in nasal volume or cross-sectional area, but ANOVA revealed a sex-dependent decrease in nasal volume over time (greater in women) irrespective of exposure condition. Exposure to *m*-xylene did not induce significant adverse changes in other parameters.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

The minimal LOAEL of 50 ppm *m*-xylene is for slight respiratory effects (reduced forced vital capacity, increased discomfort in throat and airways in females, and breathing difficulty in both sexes) and subjective symptoms of neurotoxicity (headache, dizziness, a feeling of intoxication). The LOAEL is minimal because the magnitude of the changes was small. The data were not suitable for benchmark dose analysis because a single exposure level was tested.

Uncertainty Factors used in MRL derivation: 30

[X] 3 for use of a minimal LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The database for acute-duration inhalation exposure to xylenes includes a number of studies in humans and laboratory animals. Studies in humans identify neurological and respiratory effects as the most sensitive end points for acute-duration inhalation exposure. Effects observed in humans at 50–690 ppm included irritation of the respiratory tract (breathing difficulty, discomfort in nose and throat, reduced forced air capacity), neurotoxicity (dizziness, headache, impaired short-term memory, increase in reaction times), and eye irritation (Carpenter et al. 1975a; Dudek et al. 1990; Gamberale et al. 1978; Nelson et al. 1943; NIOSH 1981). Other neurological effects in humans included altered visual evoked potentials following repeated exposure to 200 ppm *m*-xylene and impaired body balance following a single 4-hour exposure at 400 ppm (Savolainen et al. 1984; Seppalainen et al. 1989).

Acute-duration neurological effects in animals were observed at concentrations of 113 ppm and higher. These included transiently decreased operant responses in rats repeatedly exposed to 113 ppm mixed xylene (Ghosh et al. 1987), altered responses to electric shock in rats and mice exposed once to 230–320 ppm *o*-xylene (Vodickova et al. 1995), and decreased axonal transport in rats repeatedly exposed to 800 ppm mixed xylene (Padilla and Lyerly 1989). Effects related to motor incoordination were observed

following exposures to mixed xylenes or individual isomers in the range of 1,010–1,982 ppm (Carpenter et al. 1975a; De Ceaurriz et al. 1983; Korsak et al. 1988, 1990, 1993). Sensory-related changes (altered visual- or auditory-evoked potentials or hearing losses) occurred at exposures in the range of 1,400–1,600 ppm *p*-xylene (Crofton et al. 1994; Dyer et al. 1988; Pryor et al. 1987; Rebert et al. 1995). Other neurological effects included disturbances in brain catecholamine or dopamine following repeated exposure to mixed xylene or individual isomers at 2,000 ppm (Andersson et al. 1981), narcosis in rats at ≥1,940 ppm (Molnar et al. 1986), and ataxia and seizures in cats exposed to 9,500 ppm mixed xylene (Carpenter et al. 1975a).

The lowest effect levels for other end points affected by acute-duration inhalation exposure in animals were higher than the lowest LOAEL for sensitive end points in humans. Rat developmental effects (reduced fetal body weight and delayed ossification) were observed at xylene exposures in the range of 350–2000 ppm (Saillenfait et al. 2003; Ungvary et al. 1980b); maternal body weight effects were observed at 700 ppm (Ungvary et al. 1980b). Acute-duration respiratory effects in animals include decreases in lung surfactant following exposure to mixed xylenes or individual isomers at 1,000 ppm or higher (Elovaara et al. 1987; Patel et al. 1978; Toftgard and Nilsen 1982) and decreased respiratory rates in mice briefly exposed to *m*- or *o*-xylene at concentrations of 1,361–2,700 ppm (De Ceaurriz et al. 1981; Korsak et al. 1990, 1991, 1993). Increased mortality has been reported in rodents repeatedly exposed to at 700 ppm (Ungvary et al. 1980b) or once to ≥2,010 ppm (Bonnet et al. 1979; Cameron et al. 1938; Carpenter et al. 1975a; Harper et al. 1975; Hine and Zuidema 1970).

Respiratory and neurological effects are selected as co-critical effects of acute-duration inhalation exposure since they occurred at the lowest tested exposure level of 50 ppm. Ernstgard et al. (2002) was selected as the principal study for acute-duration inhalation exposure because it provides the lowest LOAEL for the co-critical effects.

Agency Contacts (Chemical Managers): Mike Fay, Ph.D.; John F. Risher, Ph.D.; Jewell D. Wilson, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Xylenes (mixed xylenes, *ortho-*, *meta-*, and *para*-xylenes)
CAS Number: 1330-20-7, 95-47-6, 108-38-3, 106-42-3
Date: August 2007
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 137
Species: Rat

Minimal Risk Level: 0.6 [ ] mg/kg/day [X] ppm
[Note: A single intermediate-duration inhalation MRL has been derived based on data for *m*-xylene that applies to mixed xylenes and all of the individual isomers. The justification for deriving a common value is that the isomers have similar toxicokinetic properties and elicit similar toxicological effects, with no isomer consistently exhibiting the greatest potency, depending on the end point. Further discussion of this rationale is presented in Section 3.2.]

Reference: Korsak Z, Wisniewska-Knypl J, Swiercz R. 1994. Toxic effects of subchronic combined exposure to n-butyl alcohol and m-xylene in rats. Int J Occup Med Environ Health 7:155-166.

Experimental design: Groups of 12–24 male Wistar rats were exposed to *m*-xylene at 0, 50, or 100 ppm, for 6 hours/day, 5 days/week for 3 months. Before the start of the study and at the end of each month of exposure, rats were examined for motor coordination (rotarod performance). The level of analgesia was tested at termination in the paw-lick response to hot-plate test at 54 °C.

Effect noted in study and corresponding doses: A dose-related increase in the failure rate on the rotarod performance test was observed. The change at 100 ppm was significantly different ($p \leq 0.05$) from controls. There was no change in severity over time. Increased sensitivity to pain was indicated by a significant decrease ($p \leq 0.05$) compared to controls in the latency of the paw-lick response at 50 and 100 ppm: 12.2±3.1, 8.7±3.8, and 8.6±2.7 seconds, respectively, for control, 50, and 100 ppm. The 50 ppm concentration of *m*-xylene is a LOAEL and serves at the basis for the intermediate inhalation MRL for xylenes.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

The low concentration of 50 ppm was a minimal LOAEL for a statistically significant decrease in the mean latency of the paw-lick response. The LOAEL is considered minimal because the effect was subtle, differing from the control by <29%, and did not significantly increase in severity with dose. The data were not suitable for benchmark dose analysis because the response was essentially a plateau.

Uncertainty Factors used in MRL derivation: 90

[X] 3 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans using dosimetric adjustment
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The minimal rat LOAEL was converted to a human equivalent following the EPA (1994) dosimetric equation for an extra-respiratory effect from an inhaled category 3 gas: minimal $LOAEL_{(HEC)}$ = minimal rat LOAEL $\times \lambda_a/\lambda_h$, where λ_a and λ_h are blood:air partition coefficients for rats and humans, respectively. Reported blood:air partition coefficients for *m*-xylene are 39.9 for Wistar rats and 26.4 for humans (Sato and Nakajima 1979). Since the rat value is higher than the human, the default value of 1 was used for λ_a/λ_h (EPA 1994). The minimal $LOAEL_{HEC}$ is therefore 50 ppm.

Was a conversion used from intermittent to continuous exposure? No. The rapid clearance of xylene from the body does not justify such a conversion.

Other additional studies or pertinent information that lend support to this MRL: The database for intermediate-duration inhalation to xylenes includes one controlled-exposure study in humans and several animal bioassays. Effects in humans exposed to 100–150 ppm *p*-xylene 1–7.5 hours/day, 5 days/week for 4 weeks included increased reporting of subjective symptoms of irritation of the nose and throat (NIOSH 1981). This study found no significant alterations in objective measures of neurological function (electroencephalography, tests of motor activity, and cognitive performance) and no alterations in pulmonary function in human subjects, but the study was limited in that some group sizes were small (n=2). Animal toxicity bioassays that tested at concentrations below 100 ppm reported no clinical signs of neurotoxicity or no adverse effects on brain weight (Hillefors-Berglund et al. 1995; Jenkins et al. 1970). In a special neurobehavioral assay, a LOAEL of 50 ppm was identified for decreased latency of the paw-lick response in rats exposed to *m*-xylene for 3 months (Korsak et al. 1994); impaired rotarod performance was noted in this study at 100 ppm, but not at 50 ppm. Other intermediate-duration studies also reported neurobehavioral effects (impaired rotarod performance, passive avoidance learning) following exposure to 100 ppm *m*-xylene for 4 weeks to 6 months (Gralewicz and Wiaderna 2001; Gralewicz et al. 1995; Korsak et al. 1994); some neurological impairment persisted for 5–9 weeks after exposure (Gralewicz and Wiaderna 2001). Other effects included distribution of astroglia cells in the brain of Mongolian gerbils exposed to 160 ppm mixed xylene for 4 months (Rosengren et al. 1986), delayed maxillary ossification and impaired rotarod performance in rats gestationally exposed to 200 ppm technical-grade xylene for 6 hours/day (Hass and Jakobsen 1993), and impaired motor coordination and spatial orientation following gestational exposure at 500 ppm (Hass et al. 1995, 1997). Neurological effects at higher concentrations included tremors in dogs exposed to 780 ppm *o*-xylene for 6 hours/day, 5 days/week for 6 weeks (Jenkins et al. 1970), alterations in brain neurotransmitters following continuous exposure to 800 ppm mixed xylenes for 30 days (Honma et al. 1983), and auditory effects in rats (mid-range hearing loss, death of hair cells of the Cochlea, or decreases in auditory brainstem responses) following exposure to ≥800 ppm mixed xylenes or 900 ppm *p*-xylene for 13 weeks (Gagnaire et al. 2001; Nylen and Hagman 1994; Pryor et al. 1987).

Non-neurological effects were observed at higher concentrations. Cardiovascular effects (increased thickness of coronary microvessels) were observed in rats exposed to 230 ppm mixed xylenes 6 hours/day, 5 days/week for 4 weeks (Morvai et al. 1987). Hepatic effects (increased liver weight) were observed at a LOAEL of 600 ppm in rats discontinuously exposed to mixed xylenes for 4 weeks (Toftgard et al. 1981). In rats exposed gestationally to mixed xylenes or *o*-xylene, a LOAEL of 500 ppm was identified for decreased fetal body weights in the absence of maternal toxicity (Bio/dynamics 1983). LOAELs for adult body weight effects were 1,000 ppm or higher (Tatrai et al. 1981). Increased deaths among squirrel monkeys and rats were noted following discontinuous intermediate-duration exposure to 780 ppm *o*-xylene (Jenkins et al. 1970), but no systemic effects were noted in rats or dogs exposed to 810 ppm mixed xylenes (Carpenter et al. 1975a).

Agency Contacts (Chemical Managers): Mike Fay, Ph.D.; John F. Risher, Ph.D.; Jewell D. Wilson, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Xylenes (mixed xylenes, *ortho-*, *meta-*, and *para*-xylenes)
CAS Number: 1330-20-7, 95-47-6, 108-38-3, 106-42-3
Date: August 2007
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 150
Species: Human

Minimal Risk Level: 0.05 [ ] mg/kg/day [X] ppm
[Note: A single chronic-duration inhalation MRL has been derived based on data for mixed xylene that applies to mixed xylenes and all of the individual isomers. The justification for deriving a common value is that the isomers have similar toxicokinetic properties and elicit similar toxicological effects, with no isomer consistently exhibiting the greatest potency, depending on the end point. Further discussion of this rationale is presented in Section 3.2.]

Reference: Uchida Y, Nakatsuka H, Ukai H, et al. 1993. Symptoms and signs in workers exposed predominantly to xylenes. Int Arch Occup Environ Health 64:597-605.

Experimental design: 175 workers (107 men, 68 women) were exposed to mixed xylenes in Chinese factories during the production of rubber boots or plastic coated wire, or in printing work. Two hundred forty-one nonexposed workers (116 men, 125 women) were recruited from the same or other factories as a comparison population. Exposures, measured with a diffusive sampler, indicated that xylenes accounted for >70% total exposure, with m-xylene accounting for 50% of the xylene exposure, followed by *p*- and *o*-xylenes. Toluene exposure and ethylbenzene exposure were about 1 and 3 ppm, respectively, with no benzene exposure. Subjects were evaluated for subjective symptoms in a questionnaire and also examined for objective parameters (serum biochemistry, hematology, and urinalysis). Exposures were corroborated by measurements of xylene metabolites in urine.

Effect noted in study and corresponding doses: The TWA (arithmetical mean) for xylenes was 21 ppm for an average of 7 years (geometric mean 14 ppm). One man was exposed to 175 ppm. Subjective symptoms included increased prevalence of anxiety, forgetfulness, inability to concentrate, eye and nasal irritation, dizziness, and sore throats. Exposure and urinary metabolites are further described in Inoue et al. (1993). The findings of hematology (red blood cell, platelet and white blood cell counts, hemoglobin), serum biochemistry (total protein, albumin, aspartate aminotransferase, alanine aminotranferase gamma-GTP, alkaline phosphatase, leucine aminopeptidase, lactate dehydrogenase, amylase, BUN, creatinine), and urinalysis were normal, indicating no liver or kidney effects. The geometric mean of 14 ppm, a LOAEL for subjective effects, is used as the basis of the chronic-duration MRL.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

The LOAEL of 14 ppm, the TWA geometric mean, was for subjective symptoms of neurotoxicity (anxiety, forgetfulness, floating sensation) and respiratory toxicity (nasal irritation and sore throat) and eye irritation. The geometric mean was chosen over the arithmetical mean because it is a better representation of central tendency. The data were not suitable for benchmark dose analysis because a single average exposure level was reported.

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Modifying Factors used in MRL derivation:

[X] 3 to account for the lack of supporting studies evaluating the chronic neurotoxicity of xylene.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No. The rapid clearance of xylene from the body does not justify such a conversion.

Other additional studies or pertinent information that lend support to this MRL: Although no other chronic-duration inhalation data are available for humans, the database for shorter duration exposures supports the findings of Uchida et al. (1993). Neurotoxicity (dizziness, headache, impaired short-term memory, increased reaction times), irritation of the respiratory tract (breathing difficulty, discomfort in nose and throat, reduced forced air capacity), and eye irritation have been reported in humans acutely exposed to ≥50 ppm *m*-xylene or mixed xylenes or ≥100 ppm *p*-xylene (Carpenter et al. 1975a; Dudek et al. 1990; Ernstgard et al. 2002; Gamberale et al. 1978; Nelson et al. 1943; NIOSH 1981). Repeated intermediate-duration exposure to ≥100 ppm *p*-xylene also increased the reporting of subjective symptoms for irritation of the nose and throat (NIOSH 1981).

Studies in animals also confirm that the nervous system is a sensitive target of inhalation exposure to xylene; respiratory function has not been assessed in animals at low concentrations. The most sensitive effects observed in acute-duration studies involved impaired neurological performance (operant responses) in rats exposed to 113 ppm mixed xylenes (Ghosh et al. 1987) and altered responses to electric shock in rats and mice exposed to 230–320 ppm *o*-xylene (Vodickova et al. 1995). The most sensitive effects in intermediate-duration studies were for increased sensitivity to pain in rats exposed to 50 ppm *m*-xylene (Korsak et al. 1994) and impairments in rotarod performance and passive avoidance learning in rats exposed to ≥100 ppm *m*-xylene (Gralewicz and Wiaderna 2001; Gralewicz et al. 1995; Korsak et al. 1994). In addition, rats exposed during gestation to ≥160 ppm mixed xylene exhibited neurological impairments after birth (degraded rotarod performance, motor coordination, and spatial orientation) (Hass and Jakobsen 1993; Hass et al. 1995; Hass et al. 1997). Conversely, the most sensitive non-neurological effects in inhalation assays in animals were developmental effects in rats acutely-exposed at 350 ppm (Ungvary et al. 1980b) and cardiovascular effects in rats exposed for an intermediate duration at 230 ppm (Morvai et al. 1987).

Acute exposure of volunteers to 50 ppm xylene and 50 ppm toluene appeared to reduce the neurological effects of xylenes (Dudek et al. 1990). Therefore, it is unlikely that the low concentration of toluene (1 ppm) reported in the Uchida et al. (1993) contributed to the observed effects.

The only other chronic-duration inhalation study was for rats exposed to 1,096 ppm *o*-xylene 8 hours/day, 7 days/week for 1 year (Tatrai et al. 1981). Hepatic changes included increases in liver weight and microsomal activity and proliferating endoplasmic reticulum, but no histopathological lesions. Body weight was reduced by 11% in exposed rats. Calculation of a chronic-duration inhalation MRL from this

rat study would not be appropriate since the study did not examine neurological effects, which are the most critical end points for inhalation exposure to xylene.

Agency Contacts (Chemical Managers): Mike Fay, Ph.D.; John F. Risher, Ph.D.; Jewell D. Wilson, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Xylenes (mixed xylenes, *ortho-*, *meta-*, and *para*-xylenes)
CAS Number: 1330-20-7, 95-47-6, 108-38-3, 106-42-3
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 20
Species: Rat

Minimal Risk Level: 1 [X] mg/kg/day [ ] ppm
[Note: A single acute-duration oral MRL has been derived based on data for *p*-xylene that applies to mixed xylenes and all of the individual isomers. The justification for deriving a common value is that the isomers have similar toxicokinetic properties and elicit similar toxicological effects, with no isomer consistently exhibiting the greatest potency, depending on the end point. Further discussion of this rationale is presented in Section 3.2.]

Reference: Dyer RS, Bercegeay MS, Mayo LM. 1988. Acute exposures to p-xylene and toluene alter visual information processing. Neurotoxicol Teratol 10:147-153.

Experimental design: Male Long-Evans rats had electrodes implanted in their skulls and were allowed to recover from surgery for 1 week prior to exposure and testing for visual processing. Two different experiments were conducted. *p*-Xylene (99.8% pure) was diluted in corn oil and administered by gavage at 1 mL/kg. Groups of 10–11 rats received single doses of *p*-xylene at doses of 0, 500, 1,000, or 2,000 mg/kg in corn oil and were tested 75 minutes later. Based on the results of this experiment, groups of 14–16 rats were dosed at 0, 125, or 250 mg/kg and tested 45 minutes later. The eyes of exposed rats were treated with topical atropine (1% in saline) 10 minutes prior to visual testing, which took place in a rectangular box with three mirrored sides. A trial consisted of the response to a single strobe-generated flash. Trials were presented at 0.3 Hz and a total of 128 trials were averaged for each flash-evoked potential. The latencies and amplitudes of the P1, N1, P2, N2, P3, and N3 waveforms were determined in the first experiment and the N3 waveform measured in the second experiment.

Effect noted in study and corresponding doses: Forty-five minutes after administration of 250 mg/kg, the amplitude of the N3 peak was decreased by 47% (statistically significant). At higher doses (500, 1,000, and 2,000 mg/kg), the N3 peak was not observed until 75 minutes after dosing. At 2,000 mg/kg, mild sedation and hypothermia (1 °C) were observed. Increased latencies were observed for the P1, N1, and P2 peaks, but this effect was attributed to the hypothermia. Effects on the N3 amplitude were still apparent 8 hours post dosing. By 16 hours post dosing, recovery was complete. Amphetamines (0.6, 1.2, or 2.5 mg/kg) produced effects on the N3 amplitude similar to *p*-xylene. The study authors suggested that the effects of xylene may be secondary to changes in arousal or excitability. No effects were noted at 125 mg/kg/day, and this NOAEL serves as the basis for the acute oral MRL for xylenes.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

The NOAEL of 125 mg/kg/day was for alteration of visual evoked potentials. The data were not suitable for benchmark dose analysis because the responses at 250 mg/kg/day (reduction in N3 peak amplitude) and ≥500 mg/kg/day (delay in N3 peak appearance) were not comparable.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Evaluation of the limited database for acute-duration oral exposure to xylenes suggests that neurotoxicity represents the most sensitive end point in laboratory animals; no quantitative human data are available. Effects observed in acute-duration, single-dose oral studies included altered visually evoked potentials in rats receiving 250 mg/kg *p*-xylene (Dyer et al. 1988) and reduced pulmonary microsomal activity in rats receiving 1,000 mg/kg *p*-xylene (Patel et al. 1978). In rats exposed 5 days/week for 2 weeks, a significant loss of Cochlear hair cells responsible for detecting midrange frequencies was observed following gavage dosing with 900 mg/kg/day *p*-xylene but not *m*- or *o*-xylene (Gagnaire and Langlais 2005). Reduced body weight gain was observed in rats following repeated dosing for 13 weeks with 1,000 mg/kg mixed xylenes or 2,000 mg/kg/day *o*- or *p*-xylene (Condie et al. 1988; NTP 1986). Repeated exposure to mixed xylenes at 2,000 mg/kg/day resulted in impaired respiration (shallow and/or labored breathing) in rats and mice and increased mortality (NTP 1986). At 2,060 mg/kg/day, developmental toxicity (cleft palate) was observed in mice gestationally exposed to mixed xylenes (Marks et al. 1982). Serious neurological effects (coma, incoordination, prostration, decreased hindleg movement) were observed in rats that received single oral gavage doses of ≥4,000 mg/kg mixed xylenes (Muralidhara and Krishnakumari 1980; NTP 1986).

The database for inhalation studies on xylene supports neurotoxicity as the sensitive target following short- or long-term exposure. Neurotoxicity was manifest as self-reported symptoms of headache, dizziness, and a feeling of intoxication in human subjects acutely-exposed to 50 ppm *m*-xylene (Ernstgard et al. 2002) and decreased operant responses in rats exposed to 113 ppm mixed xylene (Ghosh et al. 1987). Conversely, the most sensitive non-neurological effects in animals were developmental effects in rats exposed at 350 ppm (Ungvary et al. 1980b).

Neurotoxicity was selected as the critical effect for acute-duration oral exposure to xylene because it was observed at the lowest exposure level and demonstrated dose-related increases in severity. The study by Dyer et al. (1988) was selected as the principal study, since it provides the lowest LOAEL for the critical effect.

Agency Contacts (Chemical Managers): Mike Fay, Ph.D.; John F. Risher, Ph.D.; Jewell D. Wilson, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Xylenes (mixed xylenes, ortho-, meta-, and para-xylenes)
CAS Number: 1330-20-7, 95-47-6, 108-38-3, 106-42-3
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 39
Species: Mouse

Minimal Risk Level: 0.4 [X] mg/kg/day [ ] ppm
[Note: A single intermediate-duration oral MRL has been derived based on data for mixed xylenes that applies to mixed xylenes and all of the individual isomers. The justification for deriving a common value is that the isomers have similar toxicokinetic properties and elicit similar toxicological effects, with no isomer consistently exhibiting the greatest potency, depending on the end point. Further discussion of this rationale is presented in Section 3.2.]

Reference: NTP. 1986. National Toxicology Program technical report on the toxicology and carcinogenesis studies of xylenes (mixed) (60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene, and 17% ethylbenzene) (CAS No. 1330-20-7) in F344/N rats and B6C3F_1 mice (gavage studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program. NTP TR 327. NIH Publication No. 87-2583.

Experimental design: B6C3F_1 mice (50/sex/dose) were administered 500 or 1,000 mg/kg/day mixed xylenes (9.1% *o*-, 60.2% *m*-, and 13.6% *p*-xylene, and 17% ethylbenzene) in corn oil by gavage, 5 days/week for 103 weeks. Mice were observed twice daily for mortality and clinical signs; clinical signs were recorded daily for 16 months and monthly thereafter. Body weights were recorded weekly for the first 12 weeks and once a month thereafter. Animals in a moribund condition and those surviving to 103 weeks were sacrificed humanely. All animals were subjected to gross necropsy at termination; all gross lesions and a full range of tissues in each animal were examined for histopathology.

Effect noted in study and corresponding doses: There were no significant treatment-related effects of mixed xylene on body weight, survival, or the incidence of neoplastic or non-neoplastic lesions in mice receiving doses as high as 1,000 mg/kg/day, 5 days/week for 104 weeks. The only effect of treatment with mixed xylenes was hyperactivity in high-dose male and female mice, consistently observed during the half-hour period following administration in weeks 4–103. Hyperactivity observed from week 4 to week 51 is considered an overt neurological effect of intermediate-duration exposure to mixed xylene.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

The NOAEL of 500 mg/kg/day for hyperactivity in male and female mice was adjusted for intermittent exposure (5 days/7 days), resulting in a duration-adjusted NOAEL of 360 mg/kg/day. The data were not suitable for benchmark dose analysis because the incidence of hyperactivity at the LOAEL was 100% and provides no information as to the shape of the low end of dose-response curve.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Modifying Factor used in MRL derivation:

[X] 10 for the lack of testing for sensitive neurological end points and lack of developmental and multi-generational data.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Yes. The mouse NOAEL of 500 mg/kg was multiplied by 5 days/7 days, resulting in a duration-adjusted mouse NOAEL of 360 mg/kg/day.

Other additional studies or pertinent information that lend support to this MRL: The intermediate-duration oral toxicity of xylenes has been investigated in several oral gavage bioassays in rodents exposed to mixed xylene (Condie et al. 1988; NTP 1986), *m*-xylene (Elovaara et al. 1989; Wolfe 1988a), and *p*-xylene (Wolfe 1988b). The observed effects include increases in minimal chronic nephropathy and–17–37% increases in relative hepatic weight in rats exposed to ≥750 mg/kg/day mixed xylene (Condie et al. 1988); 27–46.3% increases in serum transaminase levels in rats exposed to 750–1,500 mg/kg/day mixed or *m*-xylene (Condie et al. 1988; Elovaara et al. 1989; Wolfe 1988a); reduced levels of cytochrome P-450 in the lung in rats exposed to 800 mg/kg/day *m*-xylene (Elovaara et al. 1989); 15–25% decreases in body weight gain in rats exposed to 800–1,000 mg/kg/day mixed, *m*-, or *p*-xylene (NTP 1986; Wolfe 1988a, 1988b); hyperactivity or increased aggressiveness subsequent to dosing with mixed xylene in rats at 1,500 mg/kg/day or mice at 1,000 mg/kg/day (Condie et al. 1988; NTP 1986); and 11% increased relative spleen weight, 16% increased relative kidney weight, and increased hematological effects (mild polycythemia and leukocytosis) in female rats dosed with 1,500 mg/kg/day mixed xylene (Condie et al. 1988). No hepatic effects were noted in F344 rats given mixed xylene at doses as high as 1,000 mg/kg/day or B6C3F$_1$ mice dosed at ≤2,000 mg/kg/day 5 days/week for 13 weeks (NTP 1986) or in Sprague-Dawley rats dosed with *p*-xylene at 800 mg/kg/day for 90 days (Wolfe 1988b). No renal effects were observed in rats or mice exposed to mixed xylene in studies by NTP (1986) or in rats exposed to *m*- or *p*-xylene (Wolfe 1988a, 1988b). The lack of hepatic or renal effects in some studies may be related to strain differences, exposure differences (discontinuous vs. continuous), or isomer specificities.

A limitation of standard intermediate-duration oral bioassays for xylene is that no testing was conducted for sensitive neurological effects. The only overt neurological effect of long-term exposure to xylene was hyperactivity noted in male and female mice immediately after dosing with 1,000 mg/kg (710 mg/kg/day, duration adjusted) mixed xylene beginning at week 4 of the 2-year NTP (1986) bioassay; hyperactivity was not observed at 500 mg/kg (360 mg/kg/day, duration adjusted). Neurotoxicity (hyperactivity) observed during the first year of that study (week 4–51) is selected as the critical effect of intermediate-duration exposure because it was observed at the lowest LOAEL (710 mg/kg/day, duration-adjusted).

Selection of neurotoxicity as the critical effect is consistent with the inhalation-exposure database. The most sensitive effects from inhalation exposure to xylenes were neurotoxicity: for the acute duration, self-reported symptoms of headache, dizziness, and feeling of intoxication in human subjects exposed to

50 ppm *m*-xylene (Ernstgard et al. 2002); for the intermediate duration, increased sensitivity to pain in rats exposed to 50 ppm *m*-xylene (Korsak et al. 1994); and for the chronic duration, increased reporting of symptoms of anxiety, forgetfulness, and a floating sensation in workers exposed to 14 ppm mixed xylene (Uchida et al. 1993). The most sensitive acute inhalation effect in animals was impairment of operant responses observed following exposure to ≥113 ppm *m*-xylene (Ghosh et al. 1987). Conversely, the most sensitive LOAELs for non-neurological effects in inhalation studies were for developmental effects in rats following acute exposure at ≥350 ppm (Ungvary et al. 1980b) or for cardiovascular effects in rats following intermediate exposure at ≥230 ppm (Morvai et al. 1987).

The NTP (1986) study is selected as the principal study for intermediate-duration exposure to xylene because it provides the lowest adverse effect level, a LOAEL of 710 mg/kg/day, and a NOAEL of 500 mg/kg (360 mg/kg/day, duration adjusted) for the critical effect.

Agency Contacts (Chemical Managers): Mike Fay, Ph.D.; John F. Risher, Ph.D.; Jewell D. Wilson, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Xylenes (mixed xylenes, *ortho-*, *meta-*, and *para*-xylenes)
CAS Number: 1330-20-7, 95-47-6, 108-38-3, 106-42-3
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 47
Species: Rat

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] ppm
[Note: A single chronic-duration oral MRL has been derived based on data for mixed xylenes that applies to mixed xylenes and all of the individual isomers. The justification for deriving a common value is that the isomers have similar toxicokinetic properties and elicit similar toxicological effects, with no isomer consistently exhibiting the greatest potency, depending on the end point. Further discussion of this rationale is presented in Section 3.2.]

Reference: NTP. 1986. National Toxicology Program technical report on the toxicology and carcinogenesis studies of xylenes (mixed) (60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene, and 17% ethylbenzene) (CAS No. 1330-20-7) in F344/N rats and B6C3F$_1$ mice (gavage studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program. NTP TR 327. NIH Publication No. 87-2583.

Experimental design: F344/N rats (50/sex/dose) were administered 250 or 500 mg/kg/day mixed xylenes (9.1% *o*-, 60.2% *m*-, and 13.6% *p*-xylene, and 17% ethylbenzene) in corn oil by gavage, 5 days/week for 103 weeks. Rats were observed twice daily for mortality and clinical signs; clinical signs were recorded daily for 16 months and monthly thereafter. Body weights were recorded weekly for the first 12 weeks and once a month thereafter. Animals in a moribund condition and those surviving to 103 weeks were sacrificed humanely. All animals were subjected to gross necropsy at termination; all gross lesions and a full range of tissues in each animal were examined for histopathology.

Effect noted in study and corresponding doses: No adverse effects were noted in male or female rats treated at the low dose of 250 mg/kg/day. At 500 mg/kg, body weights were 5–8% lower in male rats after week 59, but the differences from controls were not biologically significant. In addition, survival at termination was significantly lower compared to controls in male rats treated at 500 mg/kg/day. No other treatment-related non-neoplastic or neoplastic effects were observed in male or female rats.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

The MRL is based on a NOAEL of 250 mg/kg. Although no histopathology was observed in any organ, including the nervous system, in rats exposed to 500 mg/kg, this dose was not used as the basis for MRL derivation because survival was decreased in male rats at this dose level. Therefore, the next lowest dose level was used as the basis for the MRL. The NOAEL of 250 mg/kg was adjusted for intermittent exposure (5 days/7 days), resulting in a duration-adjusted NOAEL of 179 mg/kg/day. The data were not suitable for benchmark dose analysis because of the lack of measurable adverse effects aside from lethality.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Modifying Factor used in MRL derivation:

[X] 10 for the lack of testing for sensitive neurological end points and lack of developmental and multi-generational data.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Yes. The NOAEL of 250 mg/kg/day was multiplied by 5 days/7 days, resulting in a duration-adjusted NOAEL of 179 mg/kg/day.

Other additional studies or pertinent information that lend support to this MRL: In the absence of data associating health effects in humans with chronic-duration oral exposure to xylenes, the animal bioassays provide a minimal basis for deriving an MRL for humans chronically exposed to xylenes. The parallel NTP (1986) oral gavage study in $B6C3F_1$ mice reported no significant treatment-related effects of mixed xylene on body weight, survival, or the incidence of neoplastic or non-neoplastic lesions in mice receiving doses as high as 1,000 mg/kg/day, 5 days/week for 104 weeks. The only effect of treatment with mixed xylenes was hyperactivity in high-dose male and female mice, consistently observed during the half-hour period following administration in weeks 4–103.

Histopathology in specific target organs was not observed in rats or mice exposed to mixed xylene for 2 years (NTP 1986). Limitations of these studies include the lack of organ weight data, and the lack of hematology, urinalysis, or clinical chemistry data that might identify target organs for xylene. The lack of neurobehavioral analysis is also a deficiency, given that neurotoxicity was the most sensitive effect following acute-, intermediate-, or chronic-duration inhalation exposure, as well as acute-duration oral exposure to xylenes (Dyer et al. 1988; Ernstgard et al. 2002; Korsak et al. 1994; Uchida et al. 1993). The sensitive neurotoxic effects in animals were revealed by specialized neurobehavioral or neurophysiological tests and would not be apparent in standard toxicity assays.

Agency Contacts (Chemical Managers): Mike Fay, Ph.D.; John F. Risher, Ph.D.; Jewell D. Wilson, Ph.D.

This page is intentionally blank.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

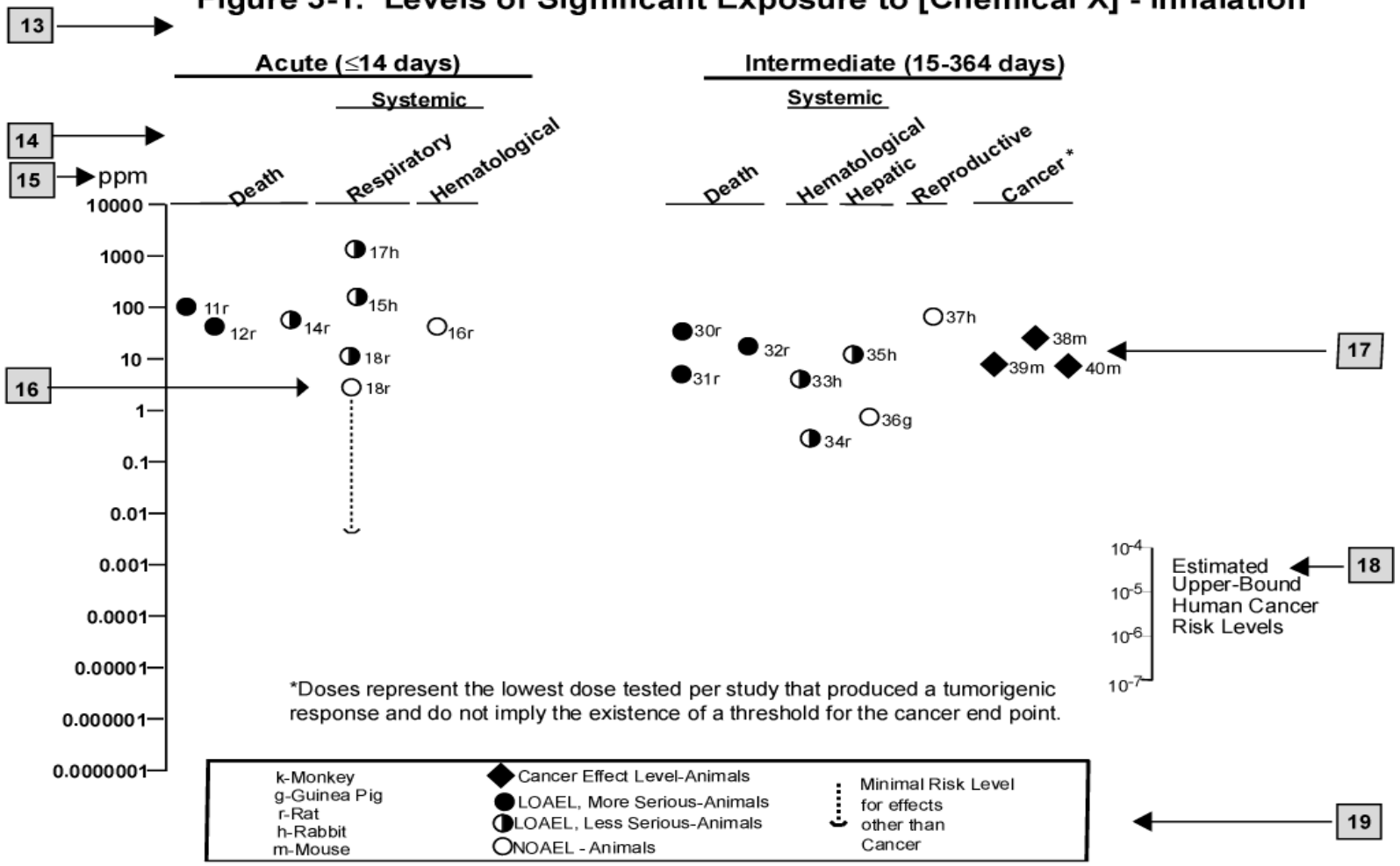
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



This page is intentionally blank.

APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

This page is intentionally blank.

APPENDIX D. INDEX